Supplementary Material

Brain Representation of Animal and Non-Animal Images in Patients with Mild Cognitive Impairment and Alzheimer's Disease

Standard Pen-and-Paper Cognitive Tests

Montreal Cognitive Assessment

Introduced in 2005, the Montreal Cognitive Assessment (MoCA) [1] is a 30-point assessment that evaluates multiple cognitive domains. It assesses executive function, visuospatial skills, calculation and abstraction, memory, language, and orientation. It can be administered in approximately 20 minutes. A higher score on the MoCA indicates better cognitive abilities. We utilized a validated version of the test specifically designed for the Iranian population in our study [2].

Addenbrooke's Cognitive Examination Revised

The Addenbrooke's Cognitive Examination Revised (ACE-R), which was revised in 2006, is an updated version of the original examination [3, 4]. It assesses multiple cognitive domains, including attention and orientation, memory, fluency, language, and visuospatial abilities. This 100-point test includes the MMSE as one of its sub-scores. Typically, it takes approximately 30 minutes to complete the test. A higher score on the ACE-R indicates better cognitive functioning. In our study, we used the validated form of the test for the Iranian population [5].

Mini-Mental State Examination

Developed in 1975, the Mini-Mental State Examination (MMSE) [6] is a cognitive test consisting of 30 points. It assesses various cognitive domains, including time and spatial orientation, registration, attention and calculation, delayed recall, language, and copying abilities. Administering the MMSE typically takes around 10 minutes. Greater cognitive abilities are associated with higher scores on the assessment. We utilized a validated version of the test specifically designed for the Iranian population in our study [7].

Psychiatric Tests

Geriatric Depression Scale

Created in 1982 [8] the Geriatric Depression Scale (GDS) is a 30-point scale used to evaluate the level of depression in elderly individuals. The higher the score on the GDS, the more advanced the stage of depression. In our research, we employed the validated version of the test designed for the Iranian population [9].

Neuropsychiatric Inventory Questionnaire

Developed in 1994 [10], the Neuropsychiatric Inventory (NPI) is a test designed to assess behavioral issues. A brief form of the NPI was developed in 2000 [11] consisting of 12 sections that evaluate symptoms including delusions, hallucinations, agitation/aggression, dysphoria/depression, anxiety, euphoria/elation, apathy/indifference, disinhibition, irritability/lability, aberrant motor activity, nighttime behavior and appetite/eating. The NPI-Q is administered to caregivers of patients, and it assigns scores based on the severity of symptoms experienced by the patient (ranging from 0 to 36) as well as the distress caused to the caregiver (ranging from 0 to 60). Lower scores on both parts indicate a better neuropsychiatric state. Conversely, higher scores indicate poorer mental health. Our study incorporated the validated test format designed for the Iranian population [12].

Functional Test

Bristol Activities of Daily Living Scale

The Bristol Activities of Daily Living Scale (BADLS) [13] was developed in 1996 and is designed to assess impairments in 20 daily self-activities including preparing food, eating, preparing drink, drinking, dressing, hygiene, teeth, bath/showering, toilet/commode, transfers, mobility, orientation-time, orientation-space, communication, telephone, housework/gardening, shopping, finances, games/hobbies, transport. A higher score on the BADLS indicates poorer functioning in daily activities and increased dependency on others.

β Estimation and Contrast Vectors

Level of brain activity or β-value in response to each individual image, in each individual voxel independent of other voxels and in each individual subject across whole brain was estimated using

general linear model (GLM) [14] in SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) within MATLAB R2015b. GLM, Equation 1, separates stimulus induced signals from noise [15] and returns the beta values. In the model, the regressors of interest were stimuli onset, while regressors of no interest included movement parameters, all convolved with the standard hemodynamic response function.

Equation 1 $$GLM: Y = X\beta + \mathcal{E}$$

The GLM consists of three primary components: Y, X, and β. Y represents the known variable, which corresponds to the BOLD signal acquired during the fMRI task. The dimensions of the Y matrix were 750 × n, where 750 signifies the total number of brain volumes acquired during functional scanning, and n signifies the total number of voxels within the subject's or standard brain. X represents the design matrix, another known variable. The dimensions of the X matrix were 750 × 390. Here, 750 covers the total number of TRs, while 390 encompasses the total number of conditions. These conditions include images of animal and non-animal, movement parameters, and constants. β stands for the unknown variable and signifies the level of brain activity for each individual voxel across various conditions, independent of other voxels.

Three different contrasts were defined. Brain activation in response to all images of animal and non-animal together, exceeding the baseline. Brain activation in response to images of animal more than non-animal. Brain activation in response to non-animals more than animals.

REFERENCES

[1] Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H (2005) The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* **53**, 695-699.

[2] Rashedi V, Foroughan M, Chehrehnegar N (2021) Psychometric properties of the Persian Montreal Cognitive Assessment in mild cognitive impairment and Alzheimer disease. *Dement Geriatr Cogn Dis Extra* **11**, 51-57.

[3] Mathuranath PS, Nestor PJ, Berrios GE, Rakowicz W, Hodges JR (2000) A brief cognitive test battery to differentiate Alzheimer's disease and frontotemporal dementia. *Neurology* **55**, 1613-1620.

[4] Mioshi E, Dawson K, Mitchell J, Arnold R, Hodges JR (2006) The Addenbrooke's Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening. *Int J Geriatr Psychiatry* **21**, 1078-1085.

[5] Pouretemad HR, Khatibi A, Ganjavi A, Shams J, Zarei M (2009) Validation of Addenbrooke's cognitive examination (ACE) in a Persian-speaking population. *Dement Geriatr Cogn Disord* **28**, 343-347.

[6] Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* **12**, 189-198.

[7] Ansari NN, Naghdi S, Hasson S, Valizadeh L, Jalaie S (2010) Validation of a Mini-Mental State Examination (MMSE) for the Persian population: a pilot study. *Appl Neuropsychol* **17**, 190-195.

[8] Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, Leirer VO (1982) Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res* **17**, 37-49.

[9] Malakouti SK, Fatollahi P, Mirabzadeh A, Salavati M, Zandi T (2006) Reliability, validity and factor structure of the GDS-15 in Iranian elderly. *Int J Geriatr Psychiatry* **21**, 588-593.

[10] Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J (1994) The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology* **44**, 2308-2314.

[11] Kaufer DI, Cummings JL, Ketchel P, Smith V, MacMillan A, Shelley T, Lopez OL, DeKosky ST (2000) Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory. *J Neuropsychiatry Clin Neurosci* **12**, 233-239.

[12] Malakouti SK, Panaghi L, Foroughan M, Salehi M, Zandi T (2012) Farsi version of the Neuropsychiatric Inventory: validity and reliability study among Iranian elderly with dementia. *Int Psychogeriatr* **24**, 223-230.

[13] Bucks RS, Ashworth DL, Wilcock GK, Siegfried K (1996) Assessment of activities of daily living in dementia: development of the Bristol Activities of Daily Living Scale. *Age Ageing* **25**, 113-120.

[14] Friston KJ, Holmes AP, Worsley KJ, Poline J-P, Frith CD, Frackowiak RSJ (1994) Statistical parametric maps in functional imaging: A general linear approach. *Hum Brain Mapp* **2**, 189-210.

[15] Monti MM (2011) Statistical analysis of fMRI time-series: a critical review of the GLM approach. *Front Hum Neurosci* **5**, 28.

Supplementary Table 1

Cortical regions with their corresponding names and coordinates in MNI space, exhibiting activation to images of animal and non-animal more than baseline within each group (p-value < 0.001, FDR corrected at 0.05). The ICA test elicits extensive brain activation in response to both animal and non-animal images.

HC	x	y	z	MCI	x	y	z	mild AD	x	y	z
R Hippocampus	22	-34	0	R ParaHippocampal Gyrus	20	-42	-10	R Superior Parietal Lobule	24	-62	50
L Fusiform Gyrus	-40	-52	-12	L Fusiform Gyrus	-32	-40	-18	L Inferior Parietal Lobule	-42	-30	42
R Fusiform Gyrus	26	-44	-12	R Fusiform Gyrus	36	-46	-18	R Inferior Parietal Lobule	40	-40	44
R Inferior Temporal Gyrus	48	-60	-12	L Inferior Temporal Gyrus	-44	-64	-10	Area hIP3 IPS	30	-52	40
R Middle Temporal Gyrus	52	-64	-2	R Inferior Temporal Gyrus	42	-64	-10	Area hIP1 IPS	-34	-42	36
R Superior Temporal Gyrus	52	-34	22	R Middle Temporal Gyrus	44	-66	6	R Postcentral Gyrus	46	-28	46
R Lingual Gyrus	22	-82	-12	R Lingual Gyrus	18	-84	-12	L Middle Occipital Gyrus	-26	-66	40
L Middle Occipital Gyrus	-14	-102	4	R Inferior Occipital Gyrus	40	-74	-8				
R Middle Occipital Gyrus	32	-68	38	L Middle Occipital Gyrus	-28	-74	28				
L Inferior Parietal Lobule	-28	-48	42	R Middle Occipital Gyrus	38	-76	12				
R Inferior Parietal Lobule	34	-52	46	L Calcarine Gyrus	4	-86	-4				
R Angular Gyrus	30	-62	44	L Insula Lobe	-30	24	-2				
L Supramarginal Gyrus	-44	-40	24	R Insula Lobe	34	24	-2				
R Insula Lobe	32	28	0	L ACC	-8	24	26				
L Insula Lobe	-32	18	10	L MCC	-4	24	32				
L ACC	-10	28	28	R MCC	6	22	30				
L Postcentral Gyrus	-36	-22	52	L Posterior-Medial Frontal	-4	-6	58				
R Postcentral Gyrus	54	-18	52	R Posterior-Medial Frontal	8	2	50				
L Precentral Gyrus	-38	-18	54	L Superior Medial Gyrus	-6	32	34				
R Precentral Gyrus	36	-22	50	R Superior Medial Gyrus	4	26	42				
L Posterior-Medial Frontal	-6	-4	54	L Middle Frontal Gyrus	-34	44	18				
R Posterior-Medial Frontal	8	-2	50	R Middle Frontal Gyrus	30	36	24				
R Superior Medial Gyrus	4	20	42	L Superior Frontal Gyrus	-20	2	52				
R IFG p. Triangularis	46	36	16	R IFG p. Orbitalis	38	30	-6				
R Precuneus	14	-66	44	L Superior Parietal Lobule	-24	-62	44				
R Cuneus	18	-66	34	L Inferior Parietal Lobule	-38	-30	36				
R Calcarine Gyrus	18	-46	4	L Precentral Gyrus	-40	4	34				
L Rolandic Operculum	-40	-22	20	R Precentral Gyrus	30	-2	48				
R Rolandic Operculum	44	-26	22	L Postcentral Gyrus	-60	-20	20				
L MCC	-2	14	42	R Postcentral Gyrus	36	-28	42				
R MCC	2	4	40	L IFG p. Opercularis	-38	4	22				
Area hIP3 IPS	30	-42	44	R IFG p. Opercularis	56	10	14				
				L Rolandic Operculum	-48	4	8				
				R Rolandic Operculum	46	6	12				